VACCINE INSIGHTS

COMMENTARY

TOPIC FOCUS • Formulation & delivery

Discovery & immunology

Adjuvanted vaccines as tools to enhance immunity and support healthy aging in older adults

Simon De Gussem, Bart Jacobs, Azhar Alhatemi, Gwenn Waerlop, Isabel Leroux-Roels, and Valentino D'Onofrio

Older adults often experience reduced vaccine responsiveness, although varying between vaccines, resulting in persistently high morbidity from infections. This is in part mediated by immunosenescence, a significant decline in immune function associated with aging. Here, we discuss the role of adjuvanted vaccines in enhancing immune responses and supporting healthy aging in older adults. Adjuvanted vaccines offer a targeted strategy to counteract these age-related immune deficits. Clinical evidence shows that MF59-adjuvanted influenza vaccines and AS01-based herpes zoster and RSV vaccines enhance immunogenicity. Mechanistically, adjuvants compensate for impaired innate signaling, improve antigen presentation, strengthen germinal center responses, and promote robust cell-mediated immunity. Beyond pathogen-specific protection, emerging data suggest potential broader benefits of adjuvanted vaccines, including effects on frailty progression, cardiovascular events, and possibly dementia, raising the hypothesis that adjuvants may improve overall immune and physiological resilience, through mechanisms not yet understood. Future research integrating mechanistic profiling with aging-relevant clinical endpoints will be essential to determine whether adjuvanted vaccines can serve as tools for healthy aging.

Vaccine Insights 2026; 5(), 249–258 · DOI: 10.18609/vac.2026.032

OLDER ADULTS MOUNT SUBOPTIMAL VACCINE RESPONSES

In the past decades, vaccination programs have profoundly reduced mortality and morbidity from infectious diseases [1]. Yet in older adults, typically defined as individuals of 65 years or older, vaccine effectiveness and immunogenicity are suboptimal [2]. This results in a persistent and substantial clinical burden of infectious diseases in this population, including influenza,

COVID-19, respiratory syncytial virus (RSV) [3], pneumococcal disease [4], and herpes zoster [5]. Adults ≥65 years account for the vast majority of influenza-related hospitalizations and deaths in high-income countries, even where vaccine coverage is high. Observational vaccine effectiveness studies report moderate protection with standard-dose influenza vaccines in this age group, with effectiveness varying across seasons and outcomes [6]. For COVID-19, observational networks documented reduced and less durable protection in older adults, with booster doses restoring but not fully eliminating the age gap [7]. In addition to chronological age, factors such as comorbidities, frailty, inflammaging, defined as chronic low-grade inflammation, and accumulated antigenic exposure over the life course modify vaccine responses in ways that standard vaccine formulations were not designed to address [2,8]. Frailty independently attenuates vaccine performance and worsens outcomes, for example vaccine effectiveness against influenza hospitalization diminishes with increasing frailty, and randomized/real-world analyses show that frail adults experience more severe complications during influenza seasons [9]. Here, we explore how adjuvanted vaccines enhance immune responses in older adults and how this potentially translates to healthy aging.

IMMUNOSENESCENCE IS A MAJOR FACTOR THAT CONTRIBUTES TO SUBOPTIMAL VACCINE RESPONSES

Aging is associated with a gradual but profound dysregulation of the immune system, which impairs the magnitude, quality, and durability of vaccine responses [2]. Immunosenescence reflects a complex remodeling of the immune system, affecting innate sensing, antigen presentation, clonal diversity as well as the generation of effective antibody and T cell-mediated responses (Figure 1) [10].

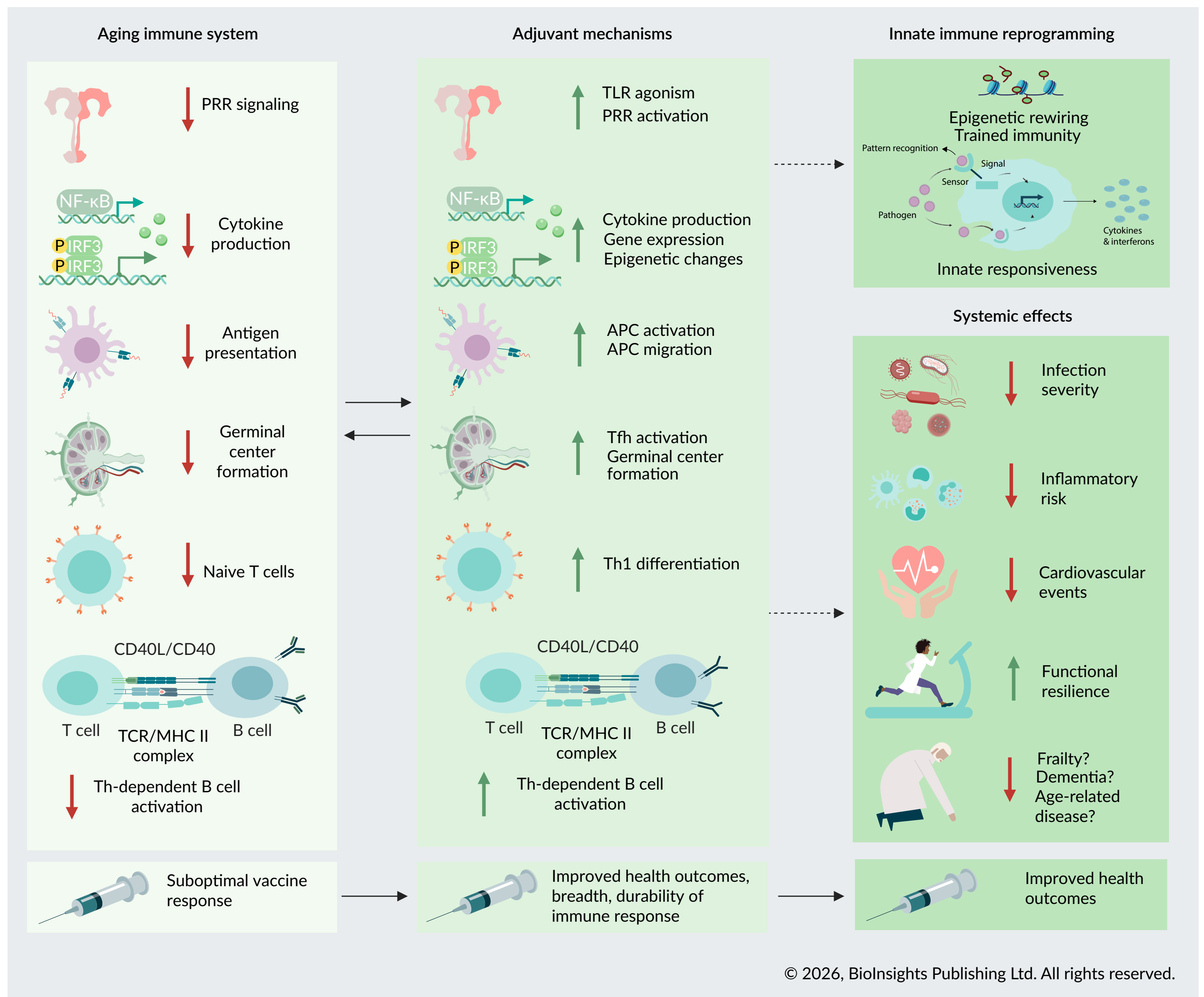
At the level of innate immunity, older adults simultaneously experience inflammaging and reduced pathogen recognition and immune signaling [11–13]. For instance, dendritic cells exhibit reduced pattern recognition receptor (PRR) signaling, diminished expression of co-stimulatory molecules, and reduced production of cytokines such as interferon-gamma (IFN-γ) and TNF-alpha (TNF-α) [14]. These changes hinder efficient antigen presentation and diminish early inflammatory signals required for robust germinal center (GC) formation and downstream adaptive responses [10].

The adaptive immune system also undergoes substantial functional and structural alterations during the aging process. Germinal centers undergo both quantitative and qualitative decline, diminishing in number and size, limiting affinity maturation and the generation of durable memory B cell responses [10]. Age-related thymic involution progressively reduces the output of naïve T lymphocytes, thereby narrowing the T cell receptor (TCR) repertoire and limiting responsiveness to novel antigens [15]. Furthermore, senescent T cells show reduced CD40 ligand (CD40L) expression, which impairs T cell-dependent B cell activation and the subsequent coordination of humoral immune responses [12]. The bone marrow similarly shows reduced B cell production, resulting in contraction of the naïve B cell repertoire. Decreased expression of activation-induced cytidine deaminase (AID) further compromises somatic hypermutation and immunoglobulin class-switch recombination in germinal centers [10].

These age-related immune changes provide a biological basis for the reduced effectiveness and durability of vaccine-induced protection in older compared with younger adults. A clearer understanding of the multifactorial nature of immunosenescence may help guide the development of more effective vaccines for older adults [16].

FIGURE 1

Conceptual framework illustrating the interaction between immunosenescence and adjuvant-induced immune activation.



© 2026, BioInsights Publishing Ltd. All rights reserved.

Conceptual framework illustrating the interaction between immunosenescence and adjuvant-induced immune activation and how this may contribute to broader systemic effects beyond pathogen-specific protection. While adjuvants enhance innate and adaptive immune responses, their potential impact on systemic outcomes such as trained immunity and healthy aging remains an area of ongoing investigation.

ADJUVANTED VACCINES INCREASE IMMUNOGENICITY & EFFICACY IN OLDER ADULTS

In recent years, several countries have implemented recommendations favoring high-dose or adjuvanted influenza vaccine formulations for older adults [17]. Both approaches have demonstrated improved clinical protection in older adults compared with standard-dose vaccines [18–20].

Influenza vaccines adjuvanted with MF59, a squalene-based emulsion in use since 1997, have demonstrated improved immunogenicity and clinical performance compared with standard-dose formulations in older adults. A systematic review and meta-analysis estimated a relative

effectiveness advantage of about 14% compared with standard-dose vaccines [19]. Additional observational studies suggest that adjuvanted influenza vaccination may also reduce cardiorespiratory and cardiovascular hospitalizations in older adults, consistent with evidence that influenza vaccination decreases major adverse cardiovascular events and all-cause mortality in high-risk populations [21].

Similarly, the AS01-adjuvanted recombinant zoster vaccine (RZV) demonstrated high efficacy across older age groups, with Phase 3 trials reporting 97.2% efficacy in adults aged ≥50 years and 89.8% efficacy in those ≥70 years [22]. Importantly, protection remained durable, with long-term follow-up studies showing sustained efficacy remaining around 90% against herpes zoster nearly ten years after vaccination [23]. In comparison, the live attenuated herpes zoster vaccine reduced the reactivation incidence by 51.3% [24].

More recently, the AS01E-adjuvanted RSV prefusion F protein vaccine demonstrated 82.6% efficacy against RSV-associated lower respiratory tract disease and 94.1% efficacy against severe disease in adults aged ≥60 years in a large Phase 3 randomized trial [25]. However, there are currently no differences observed in vaccine effectiveness between the adjuvanted RSVPreF3 and the unadjuvanted bivalent RSVpreF in the overall population aged 60 years and above [26] suggesting that differences between the vaccines may lie more in the quality or the durability of the immune responses. Indeed, the addition of the adjuvant to the RSVPreF3 antigen has been shown to impact the induction of polyfunctional CD4+ T cells [27].

IMMUNOLOGICAL MECHANISMS OF ADJUVANTS COUNTERACT IMMUNOSENESCENT DYSFUNCTION

Despite their diversity, adjuvants enhance vaccine-induced immune responses through a set of common immunological mechanisms (Figure 1). The central mechanism of action is the activation of innate immunity. Adjuvants promote the release of chemokines and cytokines that recruit monocytes, dendritic cells, and neutrophils to the injection site, facilitating efficient antigen uptake and migration of activated antigen-presenting cells (APCs) to draining lymph nodes. In parallel, they enhance APC activation, including upregulation of co-stimulatory molecules and improved antigen presentation, thereby augmenting both humoral and cellular immune responses [28–31].

Different adjuvants achieve this through distinct, but partly overlapping, pathways. Aluminum salts, used for more than a century in many licensed vaccines, are particulate adjuvants that undergo phagocytosis by immune cells, establishing a persistent intracellular depot of aluminum ions. These ions potentiate immune responses through multiple mechanistic pathways: by delaying maturation of phagosomes, elevating the production of reactive oxygen species (ROS), and metabolically reprogramming the cell toward an activated, antigen-presenting phenotype [32]. However, aluminum salts in influenza and hepatitis B vaccines have shown more limited enhancement of immune responses in older adults compared to newer adjuvants [33]. MF59 enhances antibody production and binding affinity. It additionally promotes broader epitope recognition [14]. The AS01 adjuvant system used in the RZV (AS01B) and RSV vaccine (RSVPreF3, AS01E (half dose of AS01B)) combines Monophosphoryl Lipid A (MPL; Toll-like receptor (TLR) 4 agonist) and QS-21 (a saponin), to induce strong Th1-biased cell-mediated immune responses, including early IFN-γ signaling important for MHC-II dependent antigen presentation [14]. Its liposomal formulation facilitates antigen delivery into the cytosol, which contributes to antigen presentation via the MHC-I

pathway, cross-presentation and activation of cytotoxic CD8+ T cells [14]. Other adjuvants such as MPL in AS04 (TLR4), CpG oligonucleotides (TLR9), and newer TLR4-agonist emulsions (e.g., GLA-SE) similarly act as direct TLR agonists providing defined innate immune stimuli [14].

BEYOND PATHOGEN-SPECIFIC IMMUNITY: TRAINED IMMUNITY & NON-SPECIFIC EFFECTS OF VACCINES

While the mechanisms of adjuvants are conventionally interpreted in the context of improved antigen-specific immunity, the underlying biology appears to counteract known features of immunosenescence (Figure 1) [2, 34].

In this sense, adjuvanted vaccines may be conceptualized as interventions that not only improve pathogen-specific responses but also modulate non-specific effects. Indeed, epidemiological observations across respiratory pathogens show that vaccination of older adults has effects that extend beyond preventing the infection and its direct complications.

Influenza vaccination in older adults has been associated with reductions in cardiovascular events, frailty progression, and disability, which may not be fully explained by reduced infection burden alone and could involve immune-mediated effects [35]. Although this has been observed for standard inactivated vaccines, the effects are found to be more pronounced for enhanced influenza vaccines [18]. RSV vaccines also substantially reduce hospitalizations and severe outcomes in older adults, populations in whom respiratory infections often trigger cascades of decline such as functional deterioration, decompensation of chronic diseases, and prolonged recovery trajectories [36, 37].

Emerging epidemiological observations have also suggested a possible association between herpes zoster vaccination and reduced dementia risk [38–42]. This trend appears for both the live-attenuated and RZV vaccines but was notably stronger for RZV, formulated with AS01. A similar but more modest association was also observed for the AS01E-adjuvanted RSV vaccine [43]. This may not solely reflect prevention of infection but could point to an adjuvant-driven mechanism. This signal, while preliminary and not yet mechanistically understood, reinforces the need to examine whether vaccine-induced (innate) immune responses can influence aging-relevant outcomes beyond infection alone.

More broadly, such clinical outcomes point toward a potential impact of vaccination on physiological resilience, independent of strictly antigen-specific processes.

One potential explanatory framework involves features of trained immunity [44]. Trained immunity, or innate immune memory, describes a phenomenon in which innate cells, such as monocytes, macrophages, and NK cells, undergo long-lasting functional and metabolic reprogramming, mediated in part by epigenetic modifications, following an initial stimulus, leading to heightened responsiveness to subsequent challenges [45]. This concept is best established for live-attenuated vaccines such as BCG, which have been shown to induce durable innate immune reprogramming and heterologous protection against unrelated pathogens [46]. The extent to which such processes occur in older adults following vaccination remains incompletely understood.

Evidence for similar effects following non-live vaccines or specific adjuvants is more limited and context dependent. Studies show that MF59 and AS03 can induce sustained innate immune reprogramming consistent with features of trained immunity [47,48]. However, direct evidence linking these effects to clinical outcomes in aging populations is currently lacking. Whether adjuvants contribute to the observed clinical benefits in older

adults through induction of trained immunity, improved coordination of innate and adaptive responses, or by reducing baseline inflammatory load remains an open question.

ADJUVANTED VACCINES AS TOOLS FOR HEALTHY AGING?

Given the interplay between inflammaging, immunosenescence, and chronic disease, older adults may benefit from vaccine strategies that do more than induce classical memory responses. Mounting evidence supporting (adjuvanted) vaccines in older adults suggests that their value extends beyond pathogen-specific protection, positioning them as promising immunobiological tools relevant to healthy aging [49]. While their licensed indications target specific infections, the underlying immunological mechanisms of adjuvants allow us to propose a broader hypothesis: adjuvants may promote immune and physiological resilience in older adults by coordinating innate immune function and responsiveness.

An enhancement of innate responsiveness and an innate immune reprogramming could not only explain a reduction in infection severity, but also in maladaptive inflammation, and/or an overall improvement in baseline immune coordination. This, in turn, improves balanced inflammatory control, tissue-immune communication, and enables more proportionate responses to physiological stressors. Overall, this increased immune resilience may help stabilize multiple organ systems and thereby contribute to broader systemic benefits across age, including reduced cardiovascular stress, attenuation of frailty progression, and possibly reduced risk for dementia.

This extends the conventional view of adjuvants as enhancers of antigen-specific responses and places immunization alongside other interventions aimed at maintaining physiological resilience, lowering inflammatory burden, and preserving physiological reserve.

Taken together: adjuvanted vaccines may act as tools for healthy aging by boosting innate immune function and trained immunity, with the pathogen-specific protection serving as a readout of a broader, beneficial re-tuning of the aging immune system. The mechanistic prerequisites (local innate activation, APC reprogramming, and Th1-skewing) are present, and the durability signals in older adults are encouraging for several adjuvanted platforms. The extent to which these features translate into broader systemic effects remains to be fully defined.

FUTURE RESEARCH

The clinical successes of MF59-adjuvanted influenza vaccines and AS01-based zoster and RSV vaccines in older adults suggest that targeted innate stimulation can partially overcome key features of immunosenescence. Yet the underlying mechanisms remain incompletely resolved, particularly with regard to whether adjuvants merely compensate for weak innate signaling or fundamentally re-condition aged immunity.

To transform this hypothesis into evidence, several areas warrant investigation. We need a dedicated research track to mechanistically investigate the central claim that adjuvants remodel aged innate checkpoints, and that trained immunity improves immune fitness in late life. What remains to be understood is whether the innate reprogramming they trigger extends beyond the vaccine response itself and meaningfully shifts the immunological trajectories during aging. The central task is to uncover how this trained immunity imprint interacts with the hallmarks of immunosenescence and whether it can mitigate the chronic inflammation and impaired responsiveness that characterize late-life immunity.

To answer these questions, we need

Vaccine Insights 2026; 5(), 249–258 · DOI: 10.18609/vac.2026.032

longitudinal studies in older adults coupling clinical endpoints with high-resolution single-cell epigenetic and metabolic profiling to track how adjuvants remodel innate and adaptive responses. Crucially, biological signatures should be connected to outcomes that matter for aging: frailty trajectories, disability, cardiovascular decompensation, and cognition. Comparative adjuvant trials can then identify which platforms deliver the most durable reprogramming and the best 'fit' for different aging phenotypes, with sex-, frailty- and multimorbidity-stratified enrollment to reflect real-world heterogeneity. In addition, the timing and scheduling of administration, including repeated dosing across seasons or years should be investigated as a potential determinant of durability and cumulative effects. Importantly, biological sex is an underexplored determinant of immune aging and of variability in vaccine-induced immune responses which should be systematically integrated into study design and analysis.

Ultimately, such studies will help determine whether adjuvanted vaccines should be viewed solely as enhanced immunogens, or as interventions that modulate broader aspects of immune function in aging individuals. If supported by mechanistic and clinical evidence, this paradigm would position adjuvanted vaccines as contributors to healthier immune aging, complementing their established role in pathogen-specific protection.

REFERENCES

1. Carter A, Lambach P, Hutubessy RCW, *et al.* Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. *Lancet* 2024; 403(10441), 2307–2316.
2. Hofer SJ, Rapp S, Klenerman P, Simon AK. Understanding and improving vaccine efficacy in older adults. *Nat. Aging* 2025; 5(8), 1455–1470.
3. Hanage WP, Schaffner W. Burden of acute respiratory infections caused by influenza virus, respiratory syncytial virus, and SARS-CoV-2 with consideration of older adults: a narrative review. *Infect. Dis. Ther.* 2025; 14, 5–37.
4. Blasi F, Mantero M, Santus P, Tarsia P. Understanding the burden of pneumococcal disease in adults. *Clin. Microbiol. Infect.* 2012; 18, 7–14.
5. Li J, Jin Z, Yang W, Jin M, Niu J. The global burden of varicella and herpes zoster in adults aged 65 years and older: a comprehensive analysis based on the global burden of disease 2021. *Aging Clin. Exp. Res.* 2025; 37(1), 240.
6. Ferdinands JM, Blanton LH, Alyanak E, *et al.* Protection against influenza hospitalizations from enhanced influenza vaccines among older adults: a systematic review and network meta-analysis. *J. Am. Geriatr. Soc.* 2024; 72(12), 3875–3889.
7. Mwimanzi F, Lapointe HR, Cheung PK, *et al.* Older adults mount less durable humoral responses to two doses of COVID-19 mRNA vaccine but strong initial responses to a third dose. *J. Infect. Dis.* 2022; 226(6), 983–994.
8. Andrew MK, Pott H, Staadegaard L, *et al.* Age differences in comorbidities, presenting symptoms, and outcomes of influenza illness requiring hospitalization: a worldwide perspective from the Global Influenza Hospital Surveillance Network. *Open Forum Infect. Dis.* 2023; 10(6), ofad244.
9. Andrew MK, Shinde V, Ye L, *et al.* The importance of frailty in the assessment of influenza vaccine effectiveness against influenza-related hospitalization in elderly people. *J. Infect. Dis.* 2017; 216(4), 405–414.
10. Rodrigues LP, Teixeira VR, Alencar-Silva T, *et al.* Hallmarks of aging and immunosenescence: connecting the dots. *Cytokine Growth Factor Rev.* 2021; 59, 9–21.
11. Doherty TM, Weinberger B, Didierlaurent A, Lambert PH. Age-related changes in the immune system and challenges for the development of age-specific vaccines.

Ann. Med. 2025; 57(1), 2477300.

12. Chen J, Deng JC, Goldstein DR. How aging impacts vaccine efficacy: known molecular and cellular mechanisms and future directions. *Trends Mol. Med.* 2022; 28(12), 1100–1111.
13. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* 2018; 14(10), 576–590.
14. Pereira B, Xu XN, Akbar AN. Targeting inflammation and immunosenescence to improve vaccine responses in the elderly. *Front. Immunol.* 2020; 11, 583019.
15. Lins MP, Dos Santos Reis MD. Age-related thymic involution. *Adv. Exp. Med. Biol.* 2025; 1471, 285–299.
16. Palacios-Pedrero M, Osterhaus A, Becker T, Elbahesh H, Rimmelzwaan GF, Saletti G. Aging and options to halt declining immunity to virus infections. *Front. Immunol.* 2021; 12, 681449.
17. Gavazzi G, Fougère B, Hanon O, *et al.* Enhanced influenza vaccination for older adults in Europe: a review of the current situation and expert recommendations for the future. *Expert Rev. Vaccines* 2025; 24(1), 350–364.
18. Johansen ND, Modin D, Pardo-Seco J, *et al.* Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis. *Lancet* 2025; 406(10518), 2425–2434.
19. Coleman BL, Sanderson R, Haag MDM, McGovern I. Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis. *Influenza Other Respir. Viruses* 2021; 15(6), 813–823.
20. Beran J, Reynales H, Poder A, *et al.* Prevention of influenza during mismatched seasons in older adults with an MF59-adjuvanted quadrivalent influenza vaccine: a randomised, controlled, multicentre, phase 3 efficacy study. *Lancet Infect. Dis.* 2021; 21(7), 1027–1037.
21. Lapi F, Marconi E, Simonetti M, *et al.* Adjuvanted versus nonadjuvanted influenza vaccines and risk of hospitalizations for pneumonia and cerebro/cardiovascular events in the elderly. *Expert Rev. Vaccines* 2019; 18(6), 663–670.
22. Cunningham AL, Lal H, Kovac M, *et al.* Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N. Engl. J. Med.* 2016; 375(11), 1019–1032.
23. Boutry C, Hastie A, Diez-Domingo J, *et al.* The adjuvanted recombinant zoster vaccine confers long-term protection against herpes zoster: interim results of an extension study of the pivotal phase 3 clinical trials ZOE-50 and ZOE-70. *Clin. Infect. Dis.* 2022; 74(8), 1459–1467.
24. Oxman MN, Levin MJ, Johnson GR, *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N. Engl. J. Med.* 2005; 352(22), 2271–2284.
25. Papi A, Ison MG, Langley JM, *et al.* Respiratory syncytial virus prefusion F protein vaccine in older adults. *N. Engl. J. Med.* 2023; 388(7), 595–608.
26. Payne AB, Watts JA, Mitchell PK, *et al.* Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis. *Lancet* 2024; 404(10462), 1547–1559.
27. Schwarz TF, Hwang SJ, Ylisastigui P, *et al.* Immunogenicity and safety following 1 dose of AS01E-adjuvanted respiratory syncytial virus prefusion F protein vaccine in older adults: a phase 3 trial. *J. Infect. Dis.* 2024; 230(1), e102–e110.
28. Pulendran B, Arunachalam PS, O'Hagan DT. Emerging concepts in the science of vaccine adjuvants. *Nat. Rev. Drug Discov.* 2021; 20(6), 454–475.
29. Del Giudice G, Rappuoli R, Didierlaurent AM. Correlates of adjuvanticity: a review on adjuvants in licensed vaccines. *Semin. Immunol.* 2018; 39, 14–21.
30. Olafsdottir T, Lindqvist M, Harandi AM. Molecular signatures of vaccine adjuvants. *Vaccine* 2015; 33(40), 5302–5307.
31. Zhao T, Cai Y, Jiang Y, *et al.* Vaccine adjuvants: mechanisms and platforms. *Signal Transduct. Target Ther.* 2023; 8(1), 283.
32. Danielsson R, Eriksson H. Aluminium adjuvants in vaccines – a way to modulate the immune response. *Semin. Cell Dev. Biol.* 2021; 115, 3–9.
33. Nanishi E, Angelidou A, Rotman C, *et al.* Precision vaccine adjuvants for older adults: a scoping review. *Clin. Infect. Dis.* 2022; 75,

S72–S80.

34. Lee B, Nanishi E, Levy O, Dowling DJ. Precision vaccinology approaches for the development of adjuvanted vaccines targeted to distinct vulnerable populations. *Pharmaceutics* 2023; 15(6).
35. Veronese N, Soiza RL, Michel JP. Influenza vaccination in older adults: integral to good geriatric care. *Age Ageing* 2025; 54(12).
36. Lassen MCH, Johansen ND, Christensen SH, *et al*. Bivalent RSV prefusion F protein-based vaccine for preventing cardiovascular hospitalizations in older adults: a prespecified analysis of the DAN-RSV trial. *JAMA* 2025; 334(16), 1431–1441.
37. Wiegand RE, Sung HM, Zhang Y, *et al*. Effectiveness of RSV vaccines against RSV-associated thromboembolic events. *Emerg. Infect. Dis.* 2026; 32(2), 246–249.
38. Pomirchy M, Chung S, Bommer C, Strobel S, Geldsetzer P. Herpes zoster vaccination and incident dementia in Canada: an analysis of natural experiments. *Lancet Neurol.* 2026; 25(2), 170–180.
39. Eyting M, Xie M, Michalik F, *et al*. A natural experiment on the effect of herpes zoster vaccination on dementia. *Nature* 2025; 641(8062), 438–446.
40. Pomirchy M, Bommer C, Pradella F, *et al*. Herpes zoster vaccination and dementia occurrence. *JAMA* 2025; 333(23), 2083–2092.
41. Xie M, Eyting M, Bommer C, *et al*. The effect of shingles vaccination at different stages of the dementia disease course. *Cell* 2025; 188(25), 7049–7064.
42. Rayens E, Sy LS, Qian L, *et al*. Recombinant zoster vaccine is associated with a reduced risk of dementia. *Nat. Commun.* 2026; 17(1).
43. Taquet M, Todd JA, Harrison PJ. Lower risk of dementia with AS01-adjuvanted vaccination against shingles and respiratory syncytial virus infections. *NPJ Vaccines* 2025; 10(1), 130.
44. Devine J, Jacobs B, Leroux-Roels I, *et al*. Infection, vaccination and risk of dementia: a proposed immunological model. *Front. Immunol.* 2026; 17, 1748535.
45. Ochando J, Mulder WJM, Madsen JC, Netea MG, Duivenvoorden R. Trained immunity – basic concepts and contributions to immunopathology. *Nat. Rev. Nephrol.* 2023; 19(1), 23–37.
46. Jensen KJ, Larsen N, Biering-Sørensen S, *et al*. Heterologous immunological effects of early BCG vaccination in low-birth-weight infants in Guinea-Bissau: a randomized-controlled trial. *J. Infect. Dis.* 2015; 211(6), 956–967.
47. Wimmers F, Donato M, Kuo A, *et al*. The single-cell epigenomic and transcriptional landscape of immunity to influenza vaccination. *Cell* 2021; 184(15), 3915–3935.
48. Lee A, Wimmers F, Pulendran B. Epigenetic adjuvants: durable reprogramming of the innate immune system with adjuvants. *Curr. Opin. Immunol.* 2022; 77, 102189.
49. Doherty TM, Connolly MP, Del Giudice G, *et al*. Vaccination programs for older adults in an era of demographic change. *Eur. Geriatr. Med.* 2018; 9(3), 289–300.

AFFILIATIONS

Simon De Gussem, **Bart Jacobs**, and **Azhar Alhatemi**, Center for Vaccinology, Ghent University Hospital, Ghent, Belgium

Gwenn Waerlop, Center for Vaccinology, Department of Diagnostic Sciences, Ghent University, Ghent, Belgium

Isabel Leroux-Roels and **Valentino D'Onofrio**, Center for Vaccinology, Ghent University Hospital, Ghent, Belgium & Center for Vaccinology, Department of Diagnostic Sciences, Ghent University, Ghent, Belgium

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: Isabel Leroux-Roels has received grants or research support paid to her institution from GSK, MSD, CSL Seqirus, Janssen Vaccines, Abbott, Curevac, Moderna, Virometix, Astrivax Therapeutics and Osivax for conducting vaccine trials, as well as from Janssen Vaccines, MSD, CSL Seqirus and Vifor for participation on a data safety monitoring board or advisory board.Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

AI process statement: AI tools (Claude) were used to support non-creative editorial tasks such as transcription, organization of source material, language tidying, house style checks, and reference formatting.

ARTICLE & COPYRIGHT INFORMATION

Copyright: Published by *Vaccine Insights* under Creative Commons License Deed CC BY NC ND 4.0 which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

Attribution: Copyright © 2026 Simon De Gussem, Bart Jacobs, Azhar Alhatemi, Gwenn Waerlop, Isabel Leroux-Roels, and Valentino D'Onofrio. Published by *Vaccine Insights* under Creative Commons License Deed CC BY NC ND 4.0.

Article source: This article was written by the named authors and reviewed by BioInsights' Editorial team to ensure clarity, scientific accuracy, and alignment with BioInsights' editorial standards.

Submitted for peer review: Apr 8, 2026.

Revised manuscript received: May 26, 2026.

Publication date: Jun 8, 2026.